Supplementary Online Content

Tariq R, Singh S, Gupta A, Pardi DS, Khanna S. Association of gastric acid suppression with recurrent *Clostridium difficile* infection: a systematic review and meta-analysis. *JAMA Intern Med*. Published online March 27, 2017. doi:10.1001/jamainternmed.2017.0212

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Search Strategy

#	Searches
1	*Clostridium difficile/*
2	exp Enterocolitis, Pseudomembranous/
3	exp *Clostridium* Infections/
4	(((clostridium or clostridial) adj3 (enterocolitis or enteritis or colitis or disease* or infection* or diarrhea or diarrhoea)) or "antibiotic associated colitis" or "bacillus difficilis" or "C difficile" or CDAD or clostridioses or clostridiosis or "clostridium difficile" or "clostridium difficilis" or "pseudomembranous colitis" or "pseudomembranous enteritis" or "pseudomembranous enterocolitis").mp.
5	1 or 2 or 3 or 4
6	exp Proton Pump Inhibitors/
7	("acetylsalicylic acid plus esomeprazole" or "amoxicillin plus clarithromycin plus lansoprazole" or "amoxicillin plus clarithromycin plus omeprazole" or benatoprazole or "bicarbonate plus magnesium hydroxide plus omeprazole" or "bicarbonate plus omeprazole" or "by 83178" or esomeprazole or "hydrogen potassium adenosine triphosphatase inhibitor*" or "hydrogen potassium atpase inhibitor*" or ilaprazole or lansoprazole or leminoprazole or linaprazan or nepaprazole or omeprazole or pantoprazole or picoprazole or "potassium competitive acid blocker*" or "proton pump inhibitor*" or pumaprazole or rabeprazole or revaprazan or saviprazole or soraprazan or timoprazole or vonoprazan).mp.
8	exp Histamine H2 Antagonists/
9	(algitec or burimamide or cimetidine or dalcotidine or donetidine or ebrotidine or etintidine or famotidine or "H2 antagonist*" or "H2 Antihistaminic*" or "H2 blockader*" or "H2 blocker*" or "H2 blocking agent*" or "H2 receptor antagonist*" or "H2 receptor Antihistaminic*" or "H2 Receptor Blockader*" or "H2 receptor blocker*" or "H2 receptor blocking agent*" or "histamine 2 receptor antagonist*" or "histamine 2 receptor blockader*" or "histamine 2 receptor blocker*" or "histamine 2 receptor blocking agent*" or "histamine H2 antagonist*" or "histamine H2 blockader*" or "histamine H2 blocker*" or "histamine H2 blocking agent*" or "histamine H2 receptor antagonist*" or "Histamine H2 Receptor Blockader*" or "histamine H2 receptor blocker*" or "histamine H2 receptor blocking agent*" or icotidine or "imidazolyl phenylformamidine" or lafutidine or lamtidine or lavoltidine or lupitidine or metiamide or mifentidine or niperotidine or nizatidine or osutidine or oxmetidine or pibutidine or ramixotidine or ranitidine or roxatidine or sufotidine or tiotidine or venritidine or zaltidine or zolantidine).mp.
10	6 or 7 or 8 or 9
11	5 and 10
12	exp survival/
13	exp death/
14	exp mortality/
15	mortality.fs.
16	exp survival analysis/
17	exp Recurrence/

18	(complicat* or death* or fatalit* or mortalit* or recidive or recrudescence* or recurrence* or recurrent or regenerat* or relapse* or relapsing or repeat* or serious* or severe or severity or surviv*).mp.
19	or/12-18
20	11 and 19
21	exp evidence based medicine/
22	exp meta analysis/
23	exp Meta-Analysis as Topic/
24	exp "systematic review"/
25	exp Guideline/ or exp Practice Guideline/
26	exp controlled study/
27	exp Randomized Controlled Trial/
28	exp triple blind procedure/
29	exp Double-Blind Method/
30	exp Single-Blind Method/
31	exp latin square design/
32	exp comparative study/
33	exp intervention studies/
34	exp Cross-Sectional Studies/
35	exp Cross-Over Studies/
36	exp Cohort Studies/
37	exp longitudinal study/
38	exp retrospective study/
39	exp prospective study/
40	exp clinical trial/
41	clinical study/
42	exp case-control studies/
43	exp confidence interval/
44	exp multivariate analysis/
45	((evidence adj based) or (meta adj analys*) or (systematic* adj3 review*) or guideline* or (control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo* or nocebo* or multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* adj2 study) or (intervention* adj2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or crossover or "cross-over" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") adj3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or

	"prospective analysis" or prospectiv* or "concurrent study" or "concurrent survey" or "concurrent analysis" or "clinical study" or "clinical trial" or "case control study" or "case base study" or "case referrent study" or "case referent study" or "case referent study" or "case compeer study" or "case comparison study" or "matched case control" or "multicenter study" or "multi-center study" or "odds ratio" or "confidence interval" or "change analysis" or ((study or trial or random* or control*) and compar*)).mp,pt.
46	or/21-45
47	20 and 46
48	from 20 keep 737-902
49	limit 48 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or multicenter study or observational study or randomized controlled trial or pragmatic clinical trial or comparative study or controlled clinical trial or guideline or practice guideline or meta analysis or multicenter study or observational study or randomized controlled trial or pragmatic clinical trial or systematic reviews) [Limit not valid in Embase,CCTR,CDSR; records were retained]
50	47 or 49
51	limit 50 to (editorial or erratum or letter or note or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]
52	50 not 51
53	from 20 keep 903-916
54	52 or 53
55	limit 54 to english language [Limit not valid in CDSR; records were retained]
56	limit 55 to yr="1995 -Current"
57	remove duplicates from 56

eTable 2. Newcastle-Ottawa Scoring for All Included Studies

Author, Year	Selection	Comparability	Outcome	Overall Score
Case-control studies[a]				
Abdelfatah et al (16), 2015	3	3	2	8
Cadle et al (24), 2007	3	1	2	6
Khanna et al (18), 2012	3	3	2	8
Kim et al (25), 2010	3	3	2	8
Kim et al (26), 2012	3	1	2	6
Moshkowitz et al (27), 2007	3	1	2	6
Tal et al (28), 2002	3	1	2	6
Cohort studies[b]				
Cadena et al (29), 2010	4	1	3	8
Freedberg et al (30), 2013	4	3	3	10
Hebert et al (31), 2013	4	3	3	10
Hikone et al (32), 2015	4	1	3	8
Linsky et al (33), 2010	4	3	3	10
McDonald et al (17), 2015	4	3	3	10
Rodriguez-Pardo et al (34), 2013	4	3	3	10
Samie et al (35), 2013	4	1	3	8
Weiss et al (36), 2015[c]	4	3	3	10

[a] Scoring criteria: (maximum score, 11 points)

- Selection: 1 point for each of the following:
    1. Case definition adequate with independent validation
    2. Consecutive or obviously representative series of cases
    3. Community controls
    4. No history of acid suppressive medication use among controls
- Comparability: (1 point for question 1; 2 points for question 2 [studies that adjusted for age and/or sex])
    1. All controls had no gastric acid suppression
    2. Cases and controls matched in design with adjustment of confounders
- Outcome: (1 point for each of the following):
    1. Secure records (electronic)
    2. Structured interview where blind to case/control status
    3. Same method of ascertainment for cases and controls
    4. Similar nonresponse rate for both groups

[b] Scoring criteria: (maximum score, 12 points)

- Selection: 1 point for each of the following:
    1. Somewhat representative of the average community
    2. Nonexposed from same community
    3. Secure records (electronic)
    4. Outcome of interest was not present at beginning of study
- Comparability: (1 point for question 1; 2 points for question 2 [studies that adjusted for age and/or sex])
    1. All controls had no gastric acid suppression
    2. Cases and controls matched in design with adjustment of confounders

- Outcome: 1 point for each of the following:
    1. Independent blind assessment
    2. Record linkage
    3. Follow-up long enough for outcome
    4. Complete follow-up of all subjects
    5. Subjects lost to follow-up unlikely to introduce bias, small number lost

[c] Post hoc analysis of 2 randomized controlled trials.

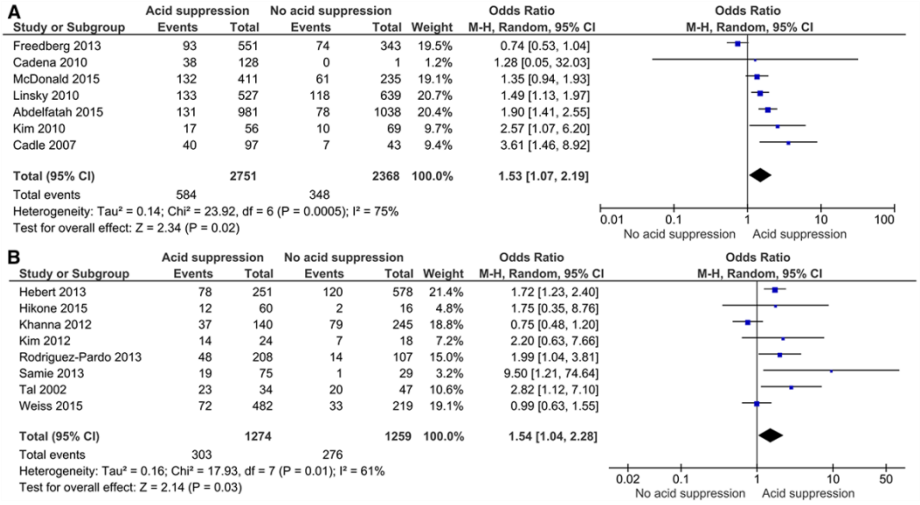
eTable 3. Covariables Adjusted in Each Study: Subgroup Analysis

Study, Year	Age	Concomitant/ Prior Antibiotics	CCI	Cortico-steroid Use	Hospital LOS	Sex	CDI Treatment	WBC Count	Chronic Kidney Disease	ICU Stay	Serum Albumin	Race/ Ethnicity
Abdelfatah et al (16), 2015	X		X	X			X		X			
Freedberg et al (30), 2013	X	X	X	X	X	X	X			X		X
Hebert et al (31), 2013	X	X			X		X			X		
Khanna et al (18), 2012	X	X	X			X						

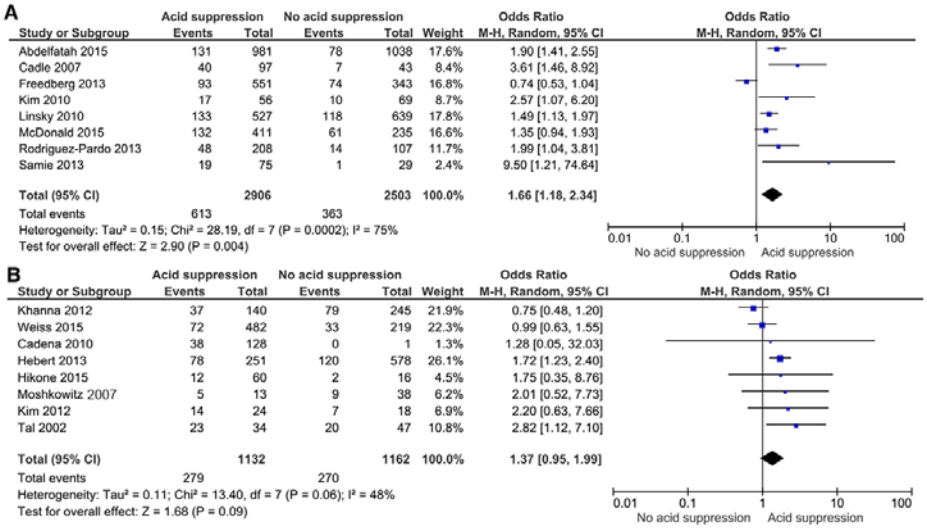
Kim et al (25), 2010	X						X	
Linsky et al (33), 2010	X	X	X	X	X			
McDonald et al (17), 2015	X	X		X	X			
Rodriguez-Pardo et al (34), 2013	X					X		
Weiss et al (36), 2015	X				X	X	X	

Abbreviations: CCI, Charlson Comorbidity Index; CDI, *Clostridium difficile* infection; ICU, intensive care unit; LOS, length of stay; WBC, white blood cell.

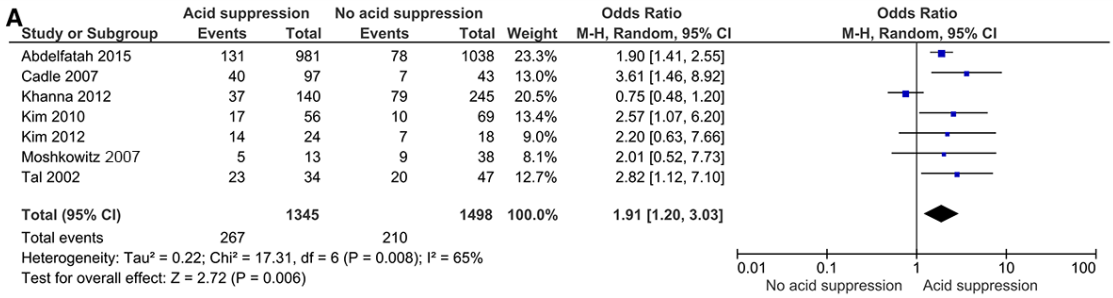
eFigure 1. Forest Plots by Definition of Recurrence. Studies demonstrating increased risk of recurrent *C difficile* infection with gastric acid suppression medication within (A) 90 days of an initial infection (OR, 1.53; 95% CI, 1.07-2.19) or (B) within 60 days of initial infection (OR, 1.54; 95% CI, 1.04-2.28) by the random-effects model. M-H indicates Mantel-Haenszel test; OR, odds ratio.

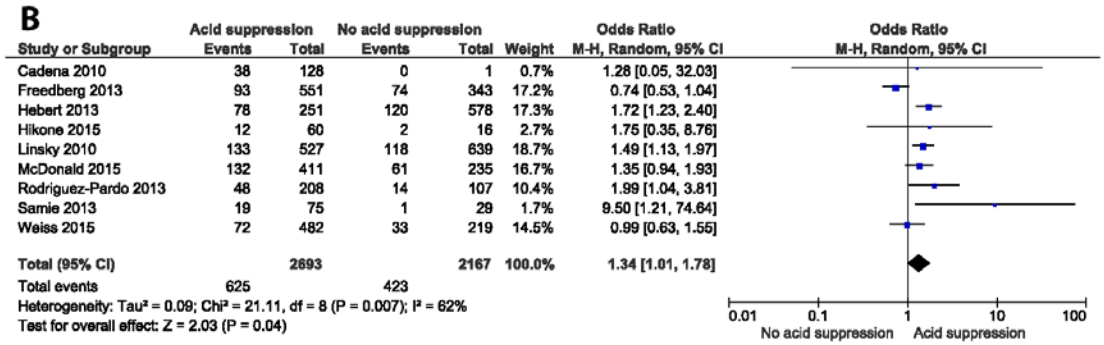


eFigure 2. Forest Plots by Type of Acid Suppression Used. Studies demonstrating increased risk of recurrent *C difficile* infection with use of (A) proton-pump inhibitors only (OR, 1.66; 95% CI, 1.18-2.34; *P*=.004) but not (B) proton-pump inhibitors and histamine-2 receptor blockers (OR, 1.37; 95% CI, 0.95-1.99) by the random-effects model. M-H indicates Mantel-Haenszel test; OR, odds ratio.

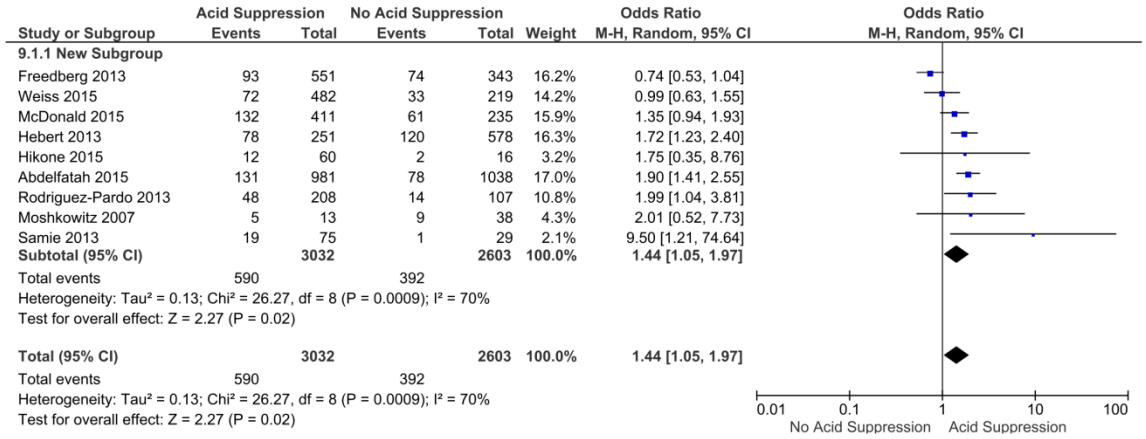


eFigure 3. Forest Plots by Type of Study. Studies demonstrating increased risk of recurrent *C difficile* infection with gastric acid suppression medication in (A) case-control studies (OR, 1.91; 95% CI, 1.20-3.03) and (B) cohort studies (OR, 1.34; 95% CI, 1.01-1.78) by the random-effects model. M-H indicates Mantel-Haenszel test; OR, odds ratio.





eFigure 4. Forest Plot of Studies in the Inpatient Setting Only. The risk of recurrent *C difficile* infection was increased with gastric acid suppression medication use among inpatients (odds ratio, 1.44; 95% CI, 1.05-1.97) by the random-effects model. M-H indicates Mantel-Haenszel test.



eFigure 5. Forest Plots by Type of Diagnostic Assay Used for *C difficile* Infection (CDI). Studies demonstrating increased risk of recurrent CDI with gastric acid suppression medication for CDI diagnosed by (A) enzyme-linked immunosorbent assay (OR, 2.54; 95% CI, 1.76-3.67) but not by (B) polymerase chain reaction (OR, 1.21; 95% CI, 0.82-1.82), by the random-effects model. M-H indicates Mantel-Haenszel test; OR, odds ratio.